

Ministry of Education and Science of Ukraine
V. N. Karazin Kharkiv National University

**METHODS OF EXAMINATION OF PATIENTS WITH
SEXUALLY TRANSMITTED DISEASES. SYPHILIS:
PATHOGEN, PATHWAYS OF INFECTION, GENERAL
COURSE, IMMUNITY, CLASSIFICATION. REINFECTION.
SUPERINFECTION. PRIMARY GENITAL SYPHILIS,
SOLID CHANCRE. CONFIRMATION OF THE DIAGNOSIS
OF PRIMARY SYPHILIS: CLINICAL AND LABORATORY**

Methodical recommendations
for independent preparation for practical classes
for the 4th year higher medical education applicants
in the discipline «Dermatology, venereology»

Electronic resource

Reviewers:

M. S. Matvienko – doctor of philosophy (medicine), associate professor, head of the department of general surgery, anesthesiology and palliative medicine;

V. D. Babazhan – Doctor of Medical Sciences, Professor of the Department of Internal Medicine No. 2, Clinical Immunology and Allergology named after Academician. L. T. Maloi, Kharkiv National Medical University.

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M 54 **Methods** of examination of patients with sexually transmitted diseases. Syphilis: pathogen, pathways of infection, general course, immunity, classification. Reinfection. Superinfection. Primary genital syphilis, solid chancre. Confirmation of the diagnosis of primary syphilis: clinical and laboratory : methodical recommendations for independent preparation for practical classes for the 4th year higher medical education applicants in the discipline «Dermatology, venereology» [Electronic resource] / compl. D. M. Dorosh, T. I. Lyadova, O. V. Volobuyeva, K. V. Pavlikova. – Kharkiv : V. N. Karazin KhNU, 2024. – (PDF 24 p.)

The methodical recommendations were developed by the team of teachers of the Department infectious diseases and clinical immunology of V. N. Karazin Kharkiv national university of the School of medicine. An indicative map of the applicants work for higher medical education is provided, with clear, consistent and detailed recommendations for preparation at each stage of the practical training. The list of basic theoretical questions and practical skills, structure and content of topics, test modules for the initial and final level of knowledge control are given, the basic and additional literature is specified, there are references to the electronic resources of department's educational materials in the annexes.

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ESTIMATED MAP OF WORK FOR HIGHER MEDICAL EDUCATION APPLICANTS FOR PRACTICAL CLASSES PREPARATION

PREPARATORY phase:	
1.	To know the interdisciplinary integration of practical classes topics with acquired theoretical knowledge and practical skills in basic disciplines (medical biology, medical and biological physics, Latin language, human anatomy, normal and pathological physiology, biological and bioorganic chemistry, pathological anatomy, microbiology, virology and immunology, pharmacology, philosophy etc.). Acknowledge the terminology (including Latin transcription).
2.	Motivational characteristic and substantiation of the topic of the practical lesson on behalf of the formation of clinical thinking , in particular for the further development of skills in knowledge application in diagnosing of the main symptoms and syndromes and the possibilities of modern laboratory and instrumental methods of internal organs examination in the process of further study and future professional work.
3.	To give better insights into the types of student's educational activity, information provided on the reference stands of the department: thematic calendar plans of lectures, practical classes and extra-curriculum independent work of the 4th year higher medical education applicants corresponding to the curriculum of the model and working program of the discipline «Dermatology, venereology».
4.	Utilization of the basic and additional educational and methodical literature : ● textbooks and tutorials (printed and electronic versions), which are listed in these guidance after the theoretical section; ● educational and methodological materials of the department (methodical recommendations for independent preparation for practical classes for the 4th year higher medical education applicants in the discipline «Dermatology, venereology» and methodological recommendations for independent student's work); ● attendance of lectures (on-site supply of the educational process using multi-media presentations during lectures) - according to the thematiccalendar plan. Usage of printed publications for classes preparation, they can be obtained from the library and / or electronic versions of it available on the official site of the V. N. Karazin KhNU http://www.univer.kharkov.ua/en/departments (navigation for sections: ... /Faculties / Departments / Infectious diseases and clinical immunology) - ref. Annex 1; and in the open interactive database of the electronic archive of the Repository of the V. N. Karazin KhNU resources

http://ekhnuir.univer.kharkov.ua (navigation: Faculty of Medicine / Educational editions, Medical Faculty) - ref. Annex 2. It is advisable to note the main issues in the form of notes	
MAIN phase: Practical classes duration is 4 academic hours, they are held at the clinical base — Municipal non-profit enterprise «State Dermatovenerologic Dispensary №1» of Kharkiv municipal council. (Kharkiv, Tsilinogradskaya Street, 50) – see Annex 3. ATTENTION! Its forbidden to attend department classes without a medical uniform, replaceable shoes, medical cap, mask, shoe covers, stethofonendoscope.	
1.	To achieve the educational goal of practical classes and mastering the theoretical part of the subject, it is necessary to LEARN and ASKNOWLEDGE the answers to the main theoretical questions of the lesson's topic (ref. to the list of the main theoretical questions) that will be checked by the lecturer through an oral and / or written survey (correction, refinement, additional answers) on the main phase of practical classes conduction.
2.	TO BE ABLE TO solve with explanations of theoretical, multiple choice (for control of the initial and final level of knowledge), situational tasks proposed for the mastering of the topic.
3.	TO MASTER PRACTICAL SKILLS on the topic • Take active part in the teacher's demonstration of the methodology of patient's examination, and to assign practical skills near the patient's bed under the supervision of a teacher. To perform the patient's examination, interpret the received laboratory and instrumental investigations data, be able to use tools needed. • Make syndromic diagnosis. To perform a differential diagnosis, to analyze the principles of the treatment, to give prescriptions for essential medicines prescribed.
4.	EXECUTE obligatory tasks foreseen for independent student work
FINAL phase:	
1.	On the basis of theoretical knowledge and practical skills mastering on the topic to form clinical thinking and syndromic diagnosis making skills for further study in the medical profession.

Purpose and main tasks of the work on the topic of the practical lesson

METHODS OF EXAMINATION OF PATIENTS WITH SEXUALLY TRANSMITTED DISEASES. SYPHILIS: PATHOGEN, PATHWAYS OF INFECTION, GENERAL COURSE, IMMUNITY, CLASSIFICATION. REINFECTION. SUPERINFECTION. PRIMARY GENITAL SYPHILIS, SOLID CHANCRE. CONFIRMATION OF THE DIAGNOSIS OF PRIMARY SYPHILIS: CLINICAL AND LABORATORY

Increase the level of knowledge on the etiology, pathogenesis, classification, clinical features and diagnosis of patients with syphilis: the main clinical and instrumental methods of examination, to teach students of higher medical education in the 4th year of training modern tactics of management of patients with venereal pathology.

MAIN QUESTIONS

As a result of studying the 4th year higher medical education applicants

must KNOW (the main theoretical questions):

1. current understanding of the etiology and pathogenesis of syphilis;
2. ways of transmission and conditions of infections, peculiarities of immunity,
3. reinfection, superinfecting with syphilis;
4. general course of syphilis in the human body;
5. factors affecting the duration and peculiarities of the incubation period of syphilis;
6. clinical signs of classical hard chancre; atypical forms of chancres;
7. characteristics and variety of clinical manifestations of primary genital syphilis.

must BE ABLE (basic practical skills on the topic of the practical lesson):

1. deontological properly collect general and sexual medical history of the patient;
2. classify the diseases, primarily transmitted sexually;
3. conduct a comprehensive examination of the patient in the proper manner;
4. analyze the results of laboratory tests of a patient with syphilis; differentiate between the clinical manifestations of the different periods of syphilis.

Tests to control the INITIAL LEVEL OF KNOWLEDGE

1. What agent causes syphilis?
 - A. *Pediculus corporis*
 - B. *Sarcoptes scabiei varietas hominis*
 - C. *Demodex folliculorum*
 - D. *Treponema pallidum*

E. Staph ilococcus albus

2. Which one of these diseases refers to classic venereal diseases?
 - A. Genital warts
 - B. Chancroid
 - C. Scabies
 - D. Pediculosis
 - E. All the above mentioned
3. The complications of hard chancre include:
 - A. Mortifying
 - B. Chancre-amygdalitis
 - C. Large chancre
 - D. Chancre-felon
 - E. Indurative edema
4. Name the atypical forms of primary syphiloma:
 - A. Balanitis, balanoposthitis
 - B. Phimosis
 - C. Indurative edema
 - D. Chancre-amygdalitis
 - E. All the above mentioned is true
5. Venereal syphilis in the human host is caused by:
 - A. *Treponema pallidum* ssp. *endemicum*.
 - B. *Treponema pallidum* ssp. *pallidum* (T. *pallidum*)
 - C. *Treponema pallidum* ssp. *Pertenue*
 - D. *Treponema carateum*
6. The most contagious stage of the syphilis is:
 - A. Primary syphilis
 - B. Secondary syphilis
 - C. Tertiary syphilis
 - D. Early latent syphilis
 - E. Late latent syphilis
7. Incubation period of primary syphilis is usually about:
 - A. 1-2 hours
 - B. 1-2 days
 - C. 1 week
 - D. 3 weeks
 - E. 5-6 months
8. Skin lesion in primary syphilis is:

- A. Macule
- B. Nodule
- C. Vesicle
- D. Ulcer
- E. Wheal

9. Chancre-amygdalitis (specific amygdalitis) is not characterized:
- A. The increase and induration of the amygdala without the formation of erosion and ulcer
 - B. Absence of pain when swallowing
 - C. Unilateral affection, the absence of violations of the general state of the body
 - D. Unilateral affection of submandibular and cervical lymph nodes
 - E. Morbidity and bilateral affection
10. Primary period of syphilis lasts for:
- A. 7-8 weeks
 - B. 14 weeks
 - C. 3-4 weeks
 - D. 3-4 months
 - E. 6 months

Standards of answers: 1–D, 2–E, 3–E, 4–D, 5–B, 6–A, 7–D, 8–D, 9–E, 10–C.

STRUCTURE AND CONTENT OF THE TOPIC

Sexually transmitted infections and diseases (STI, STD) are caused by a number of different pathogens including bacteria, viruses, fungi, and parasites.

The WHO has stated more than 20 different infectious agents transmitted by sexual contacts. Yet, there is no clear definition of STI. Infections of *T. pallidum*, *N.gonorrhea*, or *H. ducreyi* are almost always acquired by sexual contacts and cause typical venereal diseases, like lues, gonorrhea, or chancroid, while others although transmitted by sexual contacts, primarily affect organs outside the genital tract and do not result in venereal disease (HIV, HBV, CMV). Furthermore, some reports indicate sexual transmission of pathogens, which in most cases were transmitted by other routes, e.g., EBV and adenovirus. Thus, some authors prefer the term sexually transmissible infection.

According to WHO-estimates, the incidence of curable STIs has increased. Increased frequency of STIs and STDs during last years was also reported for many countries. Various reasons may account for the increase in STI-incidence, including changes of sexual behavior, lack of education, lack of prevention, traveling, increase

of predisposing conditions (like HIV infection and other STDs), increased testing (for instance through screening programs), and improved reporting of positive cases. In addition, improvement of diagnostic tests did also significantly contribute to more frequent detection of STIs.

C. trachomatis (CT) infections can be detected by a number of different methods.

Culture of *chlamydia* on cell monolayers has been the gold standard of CT diagnostics for a long time because typical intracellular inclusion bodies provide high specificity. On the other hand, dependence on vital bacteria limits sensitivity of culture. By comparing, different methods for CT detection culture were shown to have a sensitivity of at best 70–85%. Sensitivity of CT antigen tests and hybridization assays is similar to cell culture or even worse, while the highest sensitivity was demonstrated for NAATs. Thus, cell culture does not represent an appropriate reference method. Instead of culture, NAATs are now considered as gold standard for CT testing. According to CDC recommendations, NAATs are the test of choice for CT detection, while antigen tests (EIA, DFA, and rapid point-of-care tests) are no longer recommended owing to low sensitivity and low specificity.

Although some technical modifications of novel CT antigens test have improved sensitivity, detection rate in clinical specimens is still lower than for NAATs, even after using gray-zone testing. Moreover, specificity of antigen tests of 95% on an average will result in low positive predictive values (PPV) in most clinical settings, since predictive values depend on prevalence of infection. Considering a prevalence of 5%, the PPV of antigen tests with a sensitivity of 70% and a specificity of 95% is only 42.2%, in contrast to 90.6% for NAATs with a sensitivity of 95% and specificity of 99.5%. However, with lower prevalence, the PPV of NAATs will also be less than 90%. According to CDC recommendations, positive results of NAATs should be confirmed when PPV is <90%. Thus, for CT testing of low-prevalence populations (e.g. screening programs), retesting of positive samples using the same test or another NAAT would be required. A negative confirmatory test may indicate not only a false-positive result of the first test but also a false-negative result of confirmatory test. As shown recently, using one NAAT to confirm the test result of another NAAT is not suitable, owing to different sensitivities of NAATs and low amount of target in specimens, which may result in inhomogeneous distribution in aliquots.

Neisseria gonorrhoea. As described for CT, NAATs were also increasingly used for detection of *N. gonorrhoeae* (gonococci NG). In contrast to CT, traditional assays like direct examination of smears and culture are still useful for NG diagnosis. Microscopic examination of smears for NG (intracellular Gram-negative diplococci) is much more sensitive than microscopy for CT. Sensitivity of Gram staining for NG was reported to be 90% in symptomatic men, but is considerably lower in asymptomatic men (50–75%) and in women (30–50%). Direct staining of smears for CT (Giemsa) is useful only for conjunctivitis of newborns (high bacterial loads) but not suitable for detection of urogenital CT infections. Isolation of NG by culture is also easier than for CT. NG can be grown on several solid selective media.

Sensitivity of NG culture is higher than for CT cell culture and is still considered the gold standard in diagnosis of gonorrhoea. However, as for CT, isolation of NG depends on viable bacteria requiring quick transportation under optimal storage conditions.

Sensitivity of NG culture was shown to be impaired by specimen collection device, viability in transportation systems, and culture media used as well as by antibiotic (pre)treatment. Identification of NG in cultured bacteria requires confirmation by biochemical, serological, or coagulation tests. Therefore, time to results may take up to 3 days or longer. In summary, NAATs provide a number of advantages over other diagnostic tests. Besides high sensitivity and specificity, NAATs offer high flexibility, as the same specimen can be used for detection of multiple STI pathogens. All commercial companies providing NAATs for CT offer test kits, which are able to detect CT and NG simultaneously at almost the same price as for CT test kits. Usually, NAATs need only 3–5 h for up to 92 specimens; therefore, final results were obtained within one day under routine conditions. In addition, NAATs can be used for noninvasive specimens and do not require viable organisms, requiring less stringent transport conditions. Compared to swabs transported in liquid medium, dry swabs, which can be sent by mail, have been shown to be as accurate for CT/NG testing.

Syphilis, synonym lues is a chronic systemic infectious disease with a rhythmical undulating variable course, which is predominantly transmitted sexually and which affects all organs and systems of human body.

Etiology. Syphilis is caused by *Treponema pallidum* (*Treponema pallidum*), belonging to the class of *Spirochaetales*, family of *Treponemaceae*, genus of *Treponema*. It received its name because of a very poor ability to paint. *Treponema pallidum* has the form of a thin spiral of width of 0.2 μ m and a length of 5-15 μ m. Its 8- 12 curls are placed at the same distance from each other. They are very mobile and constantly carry out sliding (forward and backward), rotational, pendulum and contractile (wavy) movements. The small number of surface antigens (protein, polysaccharide, lipid) in *Treponema pallidum* determines its weak immunogenicity and helps to quite successfully counteract antibodies and lymphocytes of the human body. As facultative anaerobes *Treponema pallidum* finds the optimal conditions for its location and development in the lymphatic system. *Treponema pallidum* is unstable to drying and high temperature (at 55 °C it dies after 15-20 min.). The optimum temperature for its existence is +37 °C.

Epidemiology. Syphilitic infection occurs only in humans. According to the WHO estimates (eng - WHO) about 15 million people in the world are infected with syphilis each year. Today, the disease is considered by experts as well as a co-factor contributing to HIV - infection. Sources of infection The source of infection is the sick person, especially with infectious (active) manifestations of primary and secondary syphilis.

Ways of infection. There are three main ways of infection with syphilis: sexual - in case of genital, anal and oral contacts; professional - during surgery, instrumental examination; transfusion way -in the case of a direct penetration of *Treponema*

pallidum in the blood, particularly during blood transfusions, medical manipulations (cutting, an injection during surgery). transplacental-from sick pregnant woman to the fetus through the placenta.

Immunity. True (sterile) or artificial immunity in case of syphilis in human does not exist, as there is no natural immunity. After infection only unsterile (infectious) immunity gradually develops, which is caused by an allergic changes in the body as a result of the disease-causing agent in it. When recovering infectious immunity disappears. **Reinfection** - is recurrent disease of syphilis in human who had previously been sick with it, and did not fully recover from it, that manifested itself as the absence of any clinical symptoms, and persistent negative reaction of such person in all serological tests.

General course of syphilis and its classification. Syphilis infection is characterized by the cyclical type of clinical course which is manifested by a certain sequence of occurrence of the external symptoms, the change of periods of active and latent clinical course. In the clinical course of syphilis infection the following periods and forms are defined:

1. Incubation period- from the moment of infection to appearance of the hard chancre.

2. Primary period (syphilis I primariid) - stage of the disease from the moment of appearance of hard chancre to the development of secondary syphilides. It consists of:

- *seronegative (syphilis I seronegativa)* syphilis with persistently negative serological reactions in the presence of clinical symptoms;
- *seropositive (syphilis I seropositiva)* syphilis with positive serological reactions in the presence of clinical symptoms;
- *latent (syphilis I latens)* syphilis, which is characterized by the absence of specific clinical manifestations in patients.

3. Secondary period (syphilis II secundaria) stage of the disease, which is characterized by polymorphic rash (papules, macules, pustules) on the skin and mucous membranes and their determined staging, namely:

- *secondary recent syphilis (syphilis II recens)* - period, characterized by numerous polymorphic eruptions on the skin and mucous membranes, polyadenitis, the presence of residual symptoms of the hard chancre and strongly positive serological reactions;
- *secondary recurrent syphilis (syphilis II recediva)* period of secondary syphilis characterized by a small polymorphic grouped rash;
- *secondary latent syphilis (syphilis II latens)* - period of the disease, which is clinically latent and manifested only by positive serological reactions.

4. Third syphilis (syphilis III tertiaria) - stage, characterized by the damage of internal organs and nervous system.

5. Latent syphilis (syphilis latens). The latent syphilis includes such cases of syphilis infection, in which serological reactions are positive, but there are no clinical signs. The following variants are possible:

- premature latent syphilis (*syphilis latens praecox*), when less than two years passed from the moment of infection,
- tardive latent syphilis (*syphilis latens tarba*), when two years and more passed from the moment of infection,
- unspecified latent syphilis (*syphilis ignorata*), when the period of infection cannot be specified.

6. Congenital syphilis (*syphilis congenita*) occurs when infection with *Treponema pallidum* is caused by ill mother in the period of intrauterine growth. It is customary to distinguish the following types:

- premature congenital syphilis (*syphilis congenital praecox*) - syphilis of fetus and of children up to two years;
- tardive congenital syphilis (*syphilis congenita tarda*) in children older than two years;
- a latent congenital syphilis (*syphilis congenita latens*), in case of which the clinical manifestations are absent, and laboratory parameters of cerebrospinal fluid are normal.

7. Syphilis of nervous system (*neurosyphilis*).

General principles of diagnostics. Diagnostics of syphilis is based on: the presence of specific clinical manifestations on the skin and mucous membranes; the history data sexual contacts; the positive results of laboratory tests. If the rash elements that are not accompanied by subjective sensations are present on the skin, genitals and mucous membranes, one should think that it may be manifestations of syphilitic lesions. It is desirable to establish a patient's sexual contacts over the past few months. Spectrum of laboratory methods for diagnosis of syphilis is composed of the direct tests that detect causative agent of syphilis, or its DNA or of the large number of indirect mainly serological methods of studies.

Primary period of syphilis. Primary period of syphilis (*syphilis I primaria, lues primaria*) - stage of the disease from the appearance of primary sore (hard chancre) to the appearance of secondary syphilides. Incubation period - this is a period of development of a specific infection in the human body, which begins with the moment of infection and continues to manifestation of the first clinical signs of the disease. Its duration makes up an average of 3-4 weeks.

Clinical picture. Primary period of syphilis begins with a primary syphiloma, or hard chancre, and lasts for about 6-7 weeks before the onset of multiple lesions (secondary syphilides) on the skin and mucous membranes. 7-8 days after the formation of the hard chancre, increase in the size of lymph nodes becomes noticeable (regional scleradenitis or specific bubo). This regional scleradenitis has fairly typical symptoms: tightly elastic consistency, non-inflammatory nature, focus location, absence of cohesion of nodes with skin, their considerable mobility. Given Wasserman reaction primary period of syphilis is divided into primary sero-negative (first three weeks), and primary seropositive (following three-four weeks). In most cases, chancre is localized on the genitals. Chancre can appear on other areas of penetration of the agent (the area of the rectum, mammary gland, tunica mucosa of mouth). Hard chancre is a painless saucer-shaped ulcer or erosion, with smooth

edges without visible inflammation manifestations, on the bottom of which the infiltration of the cartilaginous hardness, or tangible induration like a thin film and shine are formed. There are clinical varieties of hard chancre depending on the number of formations, the localization of process, anatomical peculiarities of lesions (single, multiple, erosive, ulceration, genital, estragenital, large and small in size). Clinical signs of the classic hard chancre: morphological element in the form of erosion or ulceration; the bottom of the color of raw meat; the chancre is of regular round or oval form; edges are not saped, are clearly lined up, saucer-shaped and at the same level of the skin, if chancre is ulcer; size of 0.7-1.5 cm; lesion focus is painless and without inflammation swab around the periphery; chancre erosive surface is smooth and shiny; surface of the ulcer chancre has a small hemorrhage, and is sometimes covered with purulent layering; significant density of edges and bottom during palpation; skin around the elements of the rash is not changed; presence of concomitant regional scleradenitis; infiltration under erosion after its epithelization persists for several weeks, and then fully and completely resolves; ulcerative chancre heals without treatment in 6-9 weeks, leaving a hypochromic scar.

Atypical forms. There are also often atypical forms of hard chancres as indurative edema, chancre-felon and chancre-amygdalitis. Indurative edema is localized mostly on the labia - in women, as well as in the foreskin and scrotum - in men. Due to lesions of *Treponema pallidum* of lymphatic vessels, edema area increases significantly, is compacted, acquires a kind of pale pink or bluishred coloration. Chancre-felon clinically resembles an ordinary felon, is localized on the nail phalanx in the area of periungual nail wall, usually of the index finger. Finger becomes swollen, it swells in the shape of clubbell and has a bluish-red color. Chancre-felon often takes the form of a deep ulcer in the shape of a crescent, with rough edges and the bottom covered with a dirty-gray fur. Patients feel a sharp throbbing, shooting pain. The elbow and axillary lymph nodes that are often painful during palpation are increased. Chancre-amygdalitis is characterized by an increase, density and hyperemia of one tonsil with formation of neither erosion nor ulceration. The border of a redness is clear, pain is slight, overall temperature reaction is missing. Regional lymphadenitis of submandibular and cervical lymph nodes is developing. The process differs from angina by the unilateral lesion, the lack of significant pain and diffuse hyperemia of the mucous membranes of the mouth, and the general condition of the patient is normal. The clinical course of chancre can be complicated. The vulvitis, vulvovaginitis develops in women, in men balanitis (inflammation of the epithelium of the balanus), balanoposthitis (balanitis in combination with inflammation of the inner layer of the foreskin), phimosis (narrowing of the foreskin ring). Severe complications of hard chancre include mortifying.

The second clinically manifested symptom of primary period of syphilis is regional lymphadenitis. It becomes apparent at the end of the first week after ppearance of the hard chancre. Its localization is directly related to the place of the chancre appearance. For example, chancre in the genital area causes an increase of the inguinal lymph nodes. Lymph nodes gradually increase in size, become dense,

they are not painful, are not connected to each other or with the skin, are mobile; external signs of inflammation are not observed. Some (package) lymph nodes increase mainly in the area close to the lesion.

Diagnostics. Diagnosis of primary seronegative syphilis should always be confirmed by detection of *Treponema Pallidum* in secret from the surface of the hard chancre. In order to confirm the diagnosis of primary syphiloma, classic serological tests of blood, which become positive 3-4 weeks after formation of primary syphiloma, are also used. It is also important to identify the patient's sexual contacts. The main laboratory manifestations of primary syphilis are positive standard serological reactions. Wasserman reaction becomes predominantly positive in three weeks after the appearance of the hard chancre. Since that time, the primary seronegative syphilis enters the stage of primary seropositive syphilis. 4-6 weeks after the appearance of the hard chancre, symptoms indicating generalization of treponemal infection in the body appear. Almost all the lymph nodes increase, i.e., polyscleradenitis develops. At the end of the primary period of the disease, 15-20% of patients have other symptoms: increased body temperature, headache and other symptoms of general uneasiness. Primary period of syphilis ends not with healing of the hard chancre, but only with the appearance of secondary syphilides.

Direct detection of *treponema pallidum*. Dark-Field Microscopy. This photomicrograph shows the typical 'corkscrew' appearance of several *Treponema pallidum* spirochetes with the dark-field microscopy technique. *Treponema pallidum* Dark-field microscopy of lesion exudate or tissue is the definitive method for diagnosing early syphilis. *T. pallidum* cannot be viewed by normal light microscopy. Dark-field microscopy can identify *T. pallidum* with its spiral shape, 10 to 14 coils, corkscrew motion, and a total length of 6 to 20 micrometers. Dark-field microscopy is rarely used in clinical practice because most facilities do not have dark-field microscopy and most clinicians do not know how to appropriately obtain specimens. Dark-field microscopy has the potential advantage of making a definitive and rapid diagnosis of primary or secondary syphilis. Several disadvantages exist with dark-field microscopy, including

- 1) requirement for specialized, expensive equipment;
- 2) need for clinician training on how to appropriately collect and prepare a specimen for dark-field microscopy;
- 3) need for experienced microscopist who can correctly identify *T. pallidum* with dark-field microscopy;
- 4) potential false-positive results in oral specimens (from nonpathogenic spirochetes in the oral cavity);
- 5) potential false-negative results if topical agents have been applied by the patient or the specimen is not collected appropriately;
- 6) need to immediately view any collected specimen.

Clinicians need to take special precautions to protect themselves from inoculation when collecting specimens for dark-field microscopy, since the lesions contain abundant viable organisms.

Differential diagnostics. In case of differential diagnostics one shall distinguish hrd chancre from erosions or ulcers that occur in other diseases, and are also located primarily in the area of external genital organs. These include traumatic erosions, herpes rash, tuberculous ulcers, skin lesions in case of chancroid, balanitis and balanoposthitis, pyoderma chancriformis, erythroplasia of Queyrat, carcinoma of the skin. Pyoderma chancriformis is most similar to an ulcer in the primary syphiloma: it has a round or oval shape, dense infiltration, is painless, can be accompanied by concomitant scleradenitis. *Treponema pallidum* in the serum from the ulcer surface are not detectable. Serological tests for syphilis are negative. The itching and burning

sensation in the areas of future eruptions precede herpes simplex 1-2 days before the disease. Herpes is characterized by the typical small grouped vesicles with serous contents, as well as surface erosions with polycyclic contours. Chancroid has a short two-three days incubation period, is characterized by the appearance of inflammatory maculo-papules, then pustules, which soon transforms into an ulcer. After the appearance of the first ulcer (parental) as a result of auto- infection, daughter ulcers appear. The edges of these very painful ulcers are swollen, bright red, saped, abundant pus is discharged. The scrapings from the ulcer or from its edges contain streptobacillus of Dyukrey-Unna-Peterson. Erosive balanitis and balanoposthitis are manifested by the painful surface bright red erosions, without density with a thick discharge. There is no regional bubo. Chancriform itchy ecthyma is usually multiple and accompanied by acute inflammatory signs, itching and presence of other symptoms of the scabies, the lack of a density and regional scleradenitis. Traumatic erosion is mainly of linear form, accompanied by acute inflammatory signs, is painful and rapidly epithelialized, accompanying bubo is missing. Carcinoma of skin mainly occurs after the age of 45-50 years; the ulcer edges are turned out, covered with small whitish nodules, the bottom is pitted, covered with necrotic decay foci, slightly bleeding, slowly progressing with no scarring. Erythroplasia of Queyrat is manifested by the emergence of the small painless lesions on the balanus, which slowly develops, has clearly lined edges, bright red, velvety, shiny surface.

General considerations. Penicillin G, administered parenterally, is the preferred drug for treating of all stages of syphilis. The preparation(s) of penicillin used (i.e., benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of the disease. However, neither benzathine-procaine penicillin co-formulations nor oral penicillin preparations are considered appropriate for the treatment of syphilis. Reports have identified the inappropriate use of combination benzathine-procaine penicillin (Bicillin C-R) instead of the standard benzathine penicillin G (Bicillin L-A) product. Practitioners, pharmacists, and purchasing agents should be aware of the similar names of these two products and avoid use of the inappropriate combination therapy agent for treating syphilis. It is important to understand that benzathine penicillin G is slowly released from the intramuscular site due to extremely low solubility and is also hydrolyzed to penicillin G; the combination of slow absorption and hydrolysis

results in prolonged low serum levels of penicillin. In addition, practitioners should be aware of ongoing shortages of parenteral penicillin in the United States. Updated information on penicillin shortages can be found on the FDA Drug Shortages web site.

Primary and secondary syphilis. Treatment of Primary and Secondary Syphilis. Parenteral penicillin G is effective in resolving clinical symptoms associated with primary and secondary syphilis and prevents late sequelae in those who receive appropriate treatment. The recommended regimen in the 2015 STD Treatment Guidelines for adults with primary and secondary syphilis is benzathine penicillin G given as 2.4 million units intramuscular (IM) in a single dose; for infants and children, the dose is 50,000 units/kg, with a maximum of 2.4 million units. The few available studies exploring optimal dosing regimens did not find any benefit from additional doses of penicillin or with combination therapy that included other antibiotics.

Treatment of Primary or Secondary Syphilis in Penicillin-Allergic Patients. Treatment of primary and secondary syphilis for patients with documented allergy to penicillin is a topic with limited available data. Small studies and clinical experience suggest that regimens of doxycycline (100 mg orally twice daily for 14 days) or tetracycline (500 mg four times daily for 14 days) are acceptable alternatives for nonpregnant, penicillin-allergic persons who have primary or secondary syphilis. Doxycycline is preferable to tetracycline because tetracycline can cause gastrointestinal side effects and requires more frequent dosing. In addition, ceftriaxone (1-2 g daily either IM or IV for 10 to 14 days) is considered effective for treating primary and secondary syphilis, but the optimal dose and duration of ceftriaxone in this setting remains unknown.[60] Azithromycin as a single 2 g oral dose has been effective for treating primary and secondary syphilis, but concerns for emerging macrolide resistance led the CDC to recommend avoiding azithromycin for first-line syphilis treatment and, if used, it should only be considered when treatment with penicillin or doxycycline is not feasible. Further, azithromycin to treat syphilis should not be used in any circumstance to treat MSM, persons with HIV infection, or pregnant women. Any person receiving any of the alternative therapies for the treatment of syphilis should have careful clinical and serologic follow-up. Persons with a penicillin allergy for whom concern exists with adherence or follow-up should undergo penicillin desensitization and then receive treatment with benzathine penicillin G.

Test to control the FINAL LEVEL OF KNOWLEDGE

1. A 32-year-old man presents with a 4-day history of painless penile lesions. His sex partners are men and he has had 2 partners in the last 6 months. Physical examination reveals 3 non-tender ulcers on the lateral aspect of the penile shaft and firm lymphadenopathy in the right inguinal region that is nontender. Oral examination and skin inspection are normal. He has no neurologic symptoms. A clinical diagnosis of syphilis is strongly suspected; nontreponemal and treponemal

serologic tests for syphilis are ordered. Based on the information at this point, how would you clinically stage syphilis in this man?

- A. Primary syphilis
- B. Secondary syphilis
- C. Early latent syphilis
- D. Late latent syphilis

2. The duration of latency in Latent syphilis is defined by:

- A. An information received from a patient
- B. A previous negative STS
- C. 1 year
- D. A previous negative STS 6 months
- E. A previous negative STS 1 year

3. Everything A 25-years old female patient complains of swelling of the right large pudental lip and discomfort. The general condition of the patient is good, the body temperature is 36,8°C. Objective data: swelling of the right large pudental lip. It is thick, non-sensitive on palpation, with a dark-red and clear borders. The right-hand lymphadenitis is present too. Wassermann reaction is negative. What is a possible diagnosis?

- A. Limited elephantiasis
- B. Unilateral bartholinitis
- C. Indurative edema
- D. Limited Quincke's edema
- E. Cold abscess

4. Patient of the dermato-venereological department with a diagnosis of "primary seropositive syphilis" was treated with penicillin. 9 hours after the first injection a patient's body temperature rose to 38.2 °C, malaise, headache, and the maculopapular rash on skin appeared. How can these symptoms be explained?

- A. As allergic reaction
- B. As toxic reaction
- C. As idiosyncratic reaction
- D. As infectious disease
- E. As viral disease

5. A 32 years old woman complaining of neck pathology turned to the otolaryngologist. During examination: unilateral increase of the left amygdala, which caused no pain when touching to it with a spatula. The patient can not connect this kind of pathology with anything. Which is the most probable disease:

- A. Bartholinitis
- B. Seropositive primary syphilis, chancre-amygdalitis
- C. Seronegative primary syphilis, typical hard chancre

- D. Seropositive primary syphilis, indurative edema
- E. Catarrhal angina

6. A 45-year-old man is screened for syphilis and has a positive *Treponema pallidum*-specific enzyme-linked immunoassay (EIA). The laboratory performs a reflexive Rapid Plasma Reagin (RPR) test that is nonreactive. Tests for HIV, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* are negative. He has no medical problems, takes no medications, and does not use illicit drugs. He has been sexually active with the same female partner for the past 3 years. He has no prior history of any sexually transmitted infections, and has never been tested or treated for syphilis. He is asymptomatic and the physical examination is normal.

- A. What is most appropriate next step in the management of this man?
- B. Repeat both the EIA and the RPR
- C. Send an alternative nontreponemal test
- D. Send an alternative treponemal test
- E. further work-up at this time

A. A 29-year-old woman is seen in an STD clinic with vaginal discharge and is diagnosed and treated for chlamydia. Laboratory studies sent at that time show a positive treponemal enzyme immunoassay (EIA) and a positive Venereal Disease Research Laboratory (VDRL) test at a titer of 1:16. She has had four male sex partners in past 3 years. She had a negative syphilis VDRL test 5 years ago when she was pregnant, but has not had any additional syphilis testing until now. She has never been treated for syphilis and has no past or current signs or symptoms consistent with syphilis. Her physical examination is normal and a pregnancy test is negative. She does not have any antibiotic allergies. What is the best therapy for this woman?

- A. No treatment is necessary
- B. Benzathine penicillin G 2.4 million units intramuscularly in a single dose
- C. Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
- D. Ceftriaxone 1 g daily either IM for 10 days

B. A 42-year-old man is diagnosed with primary syphilis based on a non-painful genital ulcer and positive syphilis serologic tests. He reports one new male and one female sex partner in the past 90 days. Both partners are contacted and instructed to come to the clinic for evaluation. The female partner reports sexual contact with the 42-year-old man about 3 weeks ago. She has no symptoms and says she had negative testing for bacterial sexually transmitted infections (STIs) and HIV about 6 months ago. She does not have any antibiotic allergies. What would you recommend for this woman specifically related to management of her as a syphilis contact?

- A. She does not need further evaluation or treatment at this time since she is asymptomatic

- B. Order serologic tests for syphilis and treat only if the syphilis test is positive
- C. Order serologic tests for syphilis and treat with intramuscular benzathine penicillin G 2.4 million units in a single dose before results return
- D. Because the exposure occurred 3 weeks ago, defer serologic testing for syphilis for 3 more weeks and treat only if the syphilis test is positive

C. A 31-year-old man with HIV who is on antiretroviral therapy with a CD4 count of 370 cells/mm³ and an HIV RNA level less than 40 copies/mL presents with a painless ulcer in his perirectal area. He was last tested for sexually transmitted diseases, including *Neisseria gonorrhea*, *Chlamydia trachomatis*, and syphilis 12 weeks ago and all test results were negative. His repeat laboratory results on the most recent visit have returned with a positive rectal gonorrhea nucleic amplification test, a positive treponemal enzyme immunoassay (EIA), and a positive Rapid Plasma Reagin (RPR) test with a titer of 1:128. He has never been previously diagnosed with or treated for syphilis. He has no neurologic or ocular symptoms. Treatment for rectal gonorrhea is ordered. What is the recommended treatment of syphilis in this man with HIV?

- A. Amoxicillin 500 mg orally three times a day for 7 days
- B. Azithromycin 2 grams orally once
- C. Benzathine penicillin G 2.4 million units intramuscular in a single dose
- D. Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units intramuscular each at 1-week intervals

D. A 25-year-old man presents for evaluation of new nontender penile lesion. He has no other symptoms. He has no medical problems, denies medications or illicit drugs and has no antibiotic allergies. He reports insertive-only anal intercourse with multiple male partners and rare condom use. Physical examination reveals a 1 cm, nontender ulcer on the dorsal surface of his penis and no other significant findings. Further testing reveals a positive syphilis enzyme immunoassay (EIA) and a positive Rapid Plasma Reagin (RPR) at a titer of 1:32. He has never been diagnosed with or treated for syphilis in the past. An HIV test returns negative.

- A. What is the appropriate therapy for this man?
- B. Amoxicillin 500 mg orally three times a day for 7 days
- C. Azithromycin 2 grams orally once
- D. Benzathine penicillin G 2.4 million units intramuscular in a single dose
- E. Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units intramuscular each at 1-week intervals

Standards of answers: 1 – A, 2 – B, 3 – C, 4 – B, 5 – B, 6 – D, 7 – C, 8 – C, 9 – C, 10 – D.

SELF-WORK
of the 4th year higher medical education applicants
on the topic of the practical lesson

1. To provide curation of patients with a detailed history taking and complaints.
2. To give interpretation to the obtained laboratory methods of research.
3. To give interpretation to the obtained instrumental research methods.
4. Set a preliminary diagnosis during the patient's curation.

Recommended literature

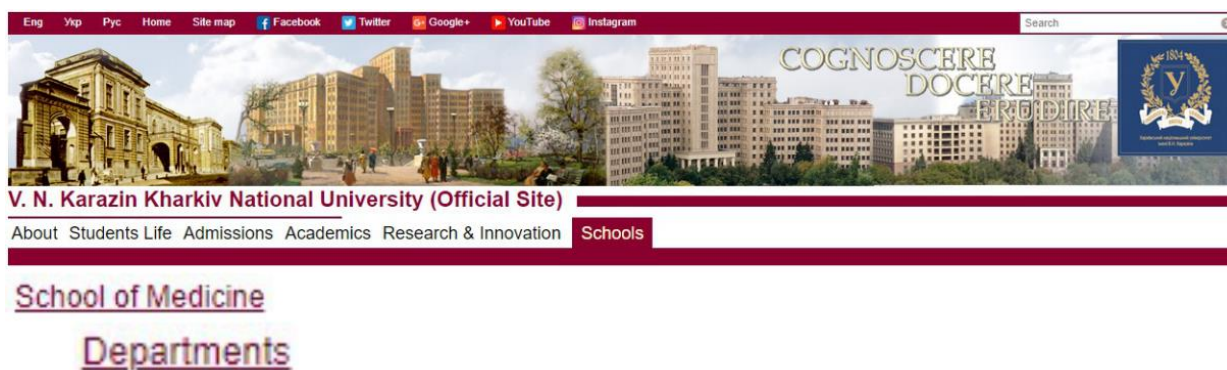
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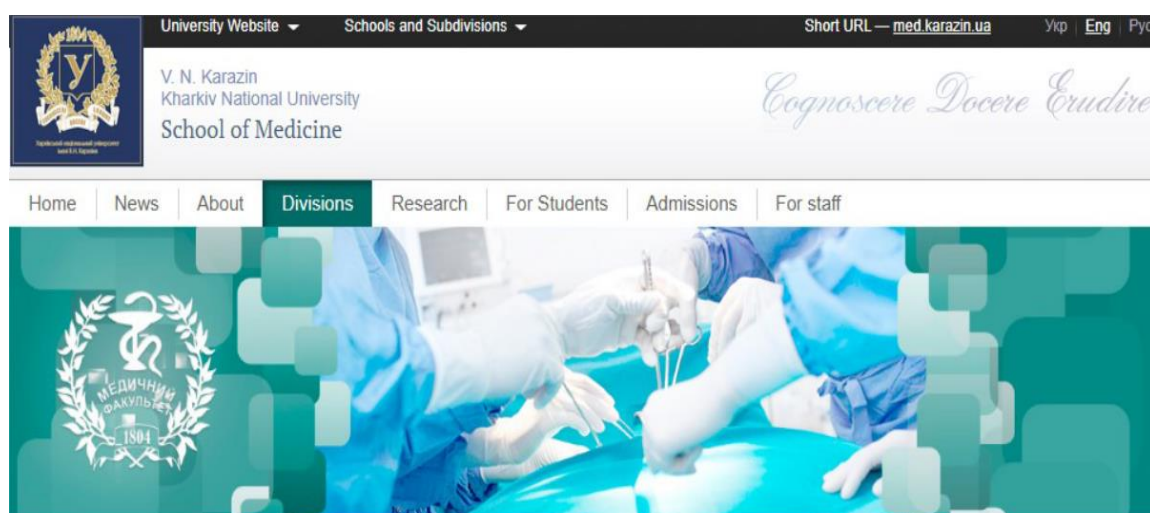
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How to get there? The clinical base of the department is located at: st. Tsilinogradskaya, 50. You can get to this place just from the city center, using the bus 245e (the bus takes passengers just near the metro "Derzhprom"), you need to get to the stop "Tsilinogradskaya", and then walk about 500 meters. You are in place! Or use the subway to the stop "Alexeyevskaya".



Електронне навчальне видання комбінованого використання
Можна використовувати в локальному та мережному режимі

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КЛІНІЧНІ ТА ЛАБОРАТОРНІ**

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для самостійної підготовки до практичних занять
здобувачів вищої медичної освіти 4-го року навчання з дисципліни
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(Англ. мовою)

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